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Focal glomerulosclerosis treated with heparin

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SUMMARY A boy with focal glomerulosclerosis as a result of nephrotic syndrome became unresponsive to corticosteroids and cyclophosphamide. He was given prolonged subcutaneous heparin with reduction in proteinuria, return of corticosteroid sensitivity, and no further deterioration (possibly improvement) in histological appearance. He remained completely well after five years.

Focal glomerulosclerosis usually progresses to death of the kidneys. It commonly presents with nephrotic syndrome, and initial histological examination may miss the focal lesions, and lead to a mistaken diagnosis of nephropathy with minimal lesions.¹ We report a 9 year old boy who presented in this way, and became unresponsive to corticosteroids and cyclophosphamide. His subsequent cure seemed to be the result of treatment with heparin.

Case report

A boy aged 9.5 years presented with severe oedema, hypoproteinaemia (total serum protein concentration 44 g/l), and a 24 hour urinary protein excretion of 1.36 g. His course is illustrated in the figure. Treatment with corticosteroids resulted in clinical remission and the disappearance of the proteinuria. Three months later he relapsed, but again responded to treatment with steroids.

After a further three months he relapsed and was referred to one of us (DRL). Prednisolone 40 mg/day was given and examination of a renal biopsy specimen under electron microscopy showed 15 glomeruli with no evidence of focal glomerulosclerosis, but evidence of fusion of the podocytes consistent with minimal change nephropathy. His urine became free of protein after six days, when cyclophosphamide 2.5 mg/kg/day was added to his treatment regimen for eight weeks. After four

weeks he relapsed; he responded to steroids but six days before completing the course of cyclophosphamide he relapsed again. A course of prednisolone did not clear his proteinuria completely, and after eight weeks reduction in dosage was attempted, but increased oedema and proteinuria required higher doses. After his sixth relapse he was given a further course of cyclophosphamide (4.8 mg/kg/day) for eight weeks.

During the next four months he became unresponsive to prednisolone 2 mg/kg/day, his urinary protein excretion remained between 4 and 11 g/day requiring intravenous courses of protein and diuretics for anasarca. Examination of a second biopsy specimen showed 31 glomeruli with widespread mild mesangial expansion, sclerosis, and hypercellularity. Discrete, sclerosing, segmental lesions were present and there was almost complete podocyte fusion. The appearance was considered typical of focal glomerulosclerosis.

After a further intravenous course of protein for anasarca it was decided to give heparin, initially intravenously for three days, but there was no obvious response. Indomethacin 25 mg three times a day for a month did not reduce the urinary protein excretion, and further intravenous protein was given.

At the age of 10.8 years a further intravenous course of heparin was given for 3.5 days, but this did not help and nephrectomy for the control of proteinuria and anasarca was considered. The parents requested a longer trial of heparin, which was then given subcutaneously for three months with a target blood concentration of 0.2 U/ml. The range achieved was 0.11 to 0.64 on an average daily dose of 550 U/kg/day. Frequent 24 hour specimens of urine were examined to determine protein excretion and these are summarised in the figure. Proteinuria rapidly decreased, and remained low but after three months the effect seemed to lessen. From day 5 fluid retention was less than it had been

Figure A patient with frequently relapsing nephrotic syndrome became unresponsive to corticosteroids. After treatment with subcutaneous heparin the concentration of protein in the urine gradually reduced, and the patient again responded to corticosteroids.

in the previous six months. On stopping the heparin proteinuria and oedema increased. After one week, at the request of the patient and parents, subcutaneous heparin was restarted. Protein excretion over 24 hours steadily declined to 70 mg after six weeks, but rose again to about half what it had been before the heparin had been given.

When heparin was stopped after three months, troublesome oedema recurred and urinary protein excretion rose to 11 g/day. Yet another course of heparin led to diminished proteinuria (lowest value 2.4 g) and easier control of fluid retention. After six months, however, anasarca requiring intravenous protein administration again developed. He was given prednisolone (2 mg/kg/day). Ten days later he had a dramatic diuresis, and the proteinuria cleared. Heparin was stopped and two days later all diuretics were withdrawn for the first time in 16 months. Serum creatinine concentrations measured before his first course of heparin and after the last course were identical at 500 $\mu\text{mol/l}$.

Two further relapses of nephrotic syndrome in the

next four months responded to short (five to seven day) courses of prednisolone. While in remission after the second episode, he was given cyclophosphamide but this was stopped after a week because of dysuria.

When he was 13 years old, 21 months after heparin was first given subcutaneously and two years after focal glomerulosclerosis was diagnosed, examination of a third biopsy specimen showed sporadic, totally obsolescent glomeruli, and mild diffuse (but variable) mesangial hypercellularity in the remainder. One of 27 glomeruli in the biopsy specimen had segmental solidification as a result of sclerosis and hyalinosis occupying about one third of the tuft. Electron microscopy showed widespread re-establishment of podocytes with only sporadic fusion.

More than five years have elapsed since the second renal biopsy specimen showed focal glomerulosclerosis. He remains well, has a full time job, and there is no evidence of proteinuria, renal failure, or hypertension.

Discussion

The course of this boy's focal glomerulosclerosis is unusual and his return to complete health seems to be as a result of treatment with heparin. Cameron *et al*² in a 9.5 year follow up of 40 consecutive patients with focal glomerulosclerosis found only four with normal renal function and no urinary protein excretion. None of the 12 children that they studied had both normal renal function and normal urine. Their actuarial analysis showed a trend for children to fare worse than adults. Those who presented with nephrotic syndrome had a poorer outcome than those who were diagnosed after biopsy specimens had been taken for proteinuria.² Our patient was both a child and presented with nephrotic syndrome.

Tejani *et al* divided their patients with nephrotic syndrome and focal glomerulosclerosis into 'steroid sensitive' and 'steroid resistant' at the outset. Those who were initially resistant reached end stage renal failure a mean (SD) of 2.3 (1.3) years earlier than those who were initially sensitive (10.5 (5.8) years).³ They could find no difference, however, in the rate of progression once focal glomerulosclerosis had been diagnosed from a biopsy specimen. Compared with their results the absence of renal failure and urinary abnormality in a patient five years after diagnosis is remarkable.

Srivastava *et al* observed that nephrotic children with late steroid resistance, focal glomerulosclerosis, and cyclophosphamide resistance constitute a group with poor prognosis.⁴ In a search of the published reports, we found only one patient with nephrosis, focal glomerulosclerosis, and resistance to steroids and alkylating agents who survived with no renal failure and no proteinuria. He was 2.5 years old at presentation and focal glomerulosclerosis was not diagnosed until he was 9.5 years old. Regrettably follow up after the diagnostic biopsy specimen was only 1.5 years.⁴

Thus on clinical grounds our child did unusually well. Strikingly, in all the papers cited where a further biopsy was carried out after the diagnostic one, progression of the focal glomerulosclerosis was found. In our case, examination of the repeat biopsy specimens did not show any progress, and it is postulated that this was due to the treatment with heparin.

The rationale for giving heparin was given in the paper by Seiler *et al* in which they reported that they had reversed the protamine induced loss of glomerular podocytes in rats by infusion of heparin.⁵ Though our patient did not have overt renal failure,

nephrectomy was considered because of his gross proteinuria and debilitating anasarca. A prolonged course of subcutaneous heparin reduced his proteinuria and fluid retention sufficiently for him to return to school, where he played soccer (in goal), and cricket (as opening batsman—with a helmet in view of the heparin induced clotting deficiency—this activity was against DRL's instructions). When the heparin was stopped, the proteinuria increased and the anasarca returned. It was largely in response to parental urging that second and third courses were given with improvement on both occasions. After the third course he became sensitive to steroids again; later examination of a biopsy specimen showed no progression, and possible improvement.

All these responses are most unusual and we suggest that heparin played a part in their occurrence. At the very least it can be claimed that heparin reduced his proteinuria, allowed a return to normal life, and bought time during which he became sensitive to corticosteroids again. It may be that heparin had a more fundamental effect on his renal lesion.

Though more studies are needed, the poor prognosis of children with focal glomerulosclerosis and its well documented recurrence in transplanted kidneys^{2,3} suggests that a trial of subcutaneous heparin may be justified in an attempt to improve the outcome of childhood nephrotic focal glomerulosclerosis.

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